

Hepatic Resection for Non-functional Neuroendocrine Liver Metastasis: Does the Presence of Unresected Primary Tumor or Extrahepatic Metastatic Disease Matter?

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ABSTRACT

Objectives. The objective of this study was to assess the impact of unresected primary tumor, as well as extrahepatic metastasis, on the long-term prognosis of patients undergoing hepatic resection for non-functional neuroendocrine liver metastasis (NF-NELM).

Methods. Patients who underwent hepatic resection for NF-NELM were identified from a multi-institutional database. Data on clinical and pathological details, as well as the long-term overall survival (OS) were obtained and compared. Propensity score matching was performed to generate matched pairs of patients.

Results. Among the 332 patients with NF-NELM, 281 (84.6%) underwent primary tumor resection, while 51

(15.4%) did not. Patients who underwent primary resection were more likely to have a pancreatic primary and meta-chronous NELM. The long-term OS of patients who did and did not have the primary neuroendocrine tumor (NET) resected was comparable on both unmatched (10-year survival rate 66.8% vs. 54.0%, $p = 0.192$) and matched (10-year survival rate 75.7% vs. 60.4%, $p = 0.271$) analyses. In contrast, patients with NF-NELM and extrahepatic metastasis had a worse OS following resection compared with patients who had intrahepatic-only metastasis on unmatched (10-year survival rate 37.5% vs. 69.3%, $p = 0.002$) and matched (10-year survival rate 37.5% vs. 86.3%, $p = 0.011$) analyses. On multivariable analysis, while resection of the primary NET was not associated with OS (hazard ratio [HR] 0.7, 95% confidence interval [CI] 0.4–1.2, $p = 0.195$), the presence of extrahepatic metastasis was independently associated with long-term risk of death (HR 3.9, 95% CI 1.7–9.2, $p = 0.002$).

Conclusions. While surgery should be considered for patients with NF-NELM who have an unresectable primary tumor, operative resection of NF-NELM may not be as beneficial in patients with extrahepatic disease.

Electronic supplementary material The online version of this article (<https://doi.org/10.1245/s10434-018-6751-8>) contains supplementary material, which is available to authorized users.

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First Received: 13 May 2018;

Published Online: 14 September 2018

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Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of rare tumors arising mainly from the pancreas and gastrointestinal tract.¹ While some GEP-NETs may have an indolent course, the liver is

a common metastatic site for GEP-NETs. In fact, up to 60–90% of patients may develop synchronous or metachronous neuroendocrine liver metastasis (NELM) during the course of their disease.

Surgical resection is the main curative treatment option for patients with NELM.² Treatment goals for NELM often include both prolongation of survival and alleviation of tumor-related symptoms, which can include debilitating hormonal symptoms and mechanical symptoms.³ While a subset of patients have functional tumors, a recent study of 9281 patients from the National Cancer Data Base with pancreatic NETs demonstrated that over 75% of NETs were non-functional.⁴ Due to the lack of early symptoms, non-functional neuroendocrine tumors with liver metastasis (NF-NELM) are often discovered late, which can result in a higher incidence of the primary lesion being unresectable and/or the presence of extrahepatic metastasis.^{4–6} NF-NETs are also more likely to be malignant and are often associated with worse outcomes versus functional NETs.^{6–9}

Traditionally, the presence of unresectable primary disease and/or extrahepatic metastatic disease was considered advanced NELM.¹⁰ While some investigators have recommended against resection of NELM in the setting of advanced disease,¹¹ other data have supported surgical debulking as a reasonable treatment of NELM that has yielded improved long-term survival.¹² As most patients with NELM die of liver failure due to intrahepatic tumor progression rather than the primary tumor or extrahepatic disease, liver resection may have a role, even in the setting of advanced disease.^{12,13} However, whether the presence of an unresectable primary tumor and/or extrahepatic metastatic disease should be considered a contraindication to liver resection for NF-NELM remains debated. As such, the objective of the current study was to define the impact of an unresected primary tumor and/or extrahepatic metastatic disease on the long-term prognosis of patients undergoing hepatic resection for NF-NELM.

METHODS

Study Cohort

A total of 548 patients who underwent liver-directed therapy for NELM from January 1980 to December 2015 were identified from nine international institutions. The Institutional Review Board of all participating institutions approved the study. The diagnoses of all NELM patients were confirmed histologically. Patients with hormonally functional NETs ($n = 201$), receipt of liver ablation only ($n = 11$), and patients who died within 30 days after surgery ($n = 4$) were excluded.

Data Collection and Follow-Up

Data on clinical, operative, and pathological details were collected for each patient at each institution in a standardized database pertaining to both the primary tumor and liver metastases. Extrahepatic metastatic disease was determined by imaging studies, e.g. computed tomography (CT) scan, octreoscan, positron emission tomography (PET)-CT, etc., and/or biopsy before surgery among the different centers. Grade of tumor differentiation was classified as well (G0), moderate (G1), or poor (G3) according to the 2010 WHO grading system.¹⁴ An R0 resection was defined as the absence of macroscopic or microscopic disease at the surgical margin, while an R1 resection was defined as the microscopic presence of tumor and R2 was classified as macroscopic presence of tumor.¹⁵

Statistical Analysis

Continuous variables were expressed as medians with interquartile ranges (IQRs), while categorical variables were reported as totals and frequencies. Univariable comparisons were assessed by using the Mann–Whitney U test, Chi square test, or Fisher exact test, as appropriate. Survival was evaluated using Kaplan–Meier curves and median values were compared using the log-rank tests. The impact of various clinicopathological factors on overall survival (OS) was assessed using a Cox proportional hazards model and expressed as hazard ratio (HR) and 95% confidence interval (CI). Factors with a p value < 0.05 by univariate analysis were included in the multivariate analysis. Propensity score matching (PSM) was used to adjust for differences in baseline characteristics between groups. In all analyses, a p value < 0.05 (two-tailed) was considered statistically significant. Statistical analyses were performed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Demographic and Clinicopathological Characteristics

Among the 548 patients diagnosed with GEP-NETs, a total of 332 (60.6%) patients who underwent hepatectomy for NF-NELM were included in the analytic cohort (Table 1). Median patient age was 58 years (IQR 49–67) and nearly half of patients were female ($n = 151$, 45.5%). Among all patients, 187 (56.3%) presented with non-specific clinical symptoms, including abdominal cramping. Primary tumor site included the pancreas ($n = 149$, 44.9%), gastrointestinal tract ($n = 129$, 38.8%), tracheobronchial and lung ($n = 14$, 4.2%), and unknown location ($n = 40$, 12%). Liver metastases were synchronous in 217 (65.4%)

TABLE 1 Clinicopathological characteristics of patients who underwent hepatic resection for non-functional neuroendocrine liver metastasis

	All patients (<i>n</i> = 332)	Primary resected (<i>n</i> = 281)	Primary unresected (<i>n</i> = 51)	<i>p</i> Value
Age, years (IQR)	58 (49–67)	58 (49–67)	48 (42–67)	0.863
Sex, male/female	181 (54.5)/151 (45.5)	160 (56.9)/121 (43.1)	21 (41.2)/30 (58.8)	0.038
Symptomatic	187 (56.3)	164 (58.4)	23 (45.1)	0.079
Primary tumor location				< 0.001
Non-pancreatic	183 (55.1)	137 (48.8)	46 (90.2)	
Pancreatic	149 (44.9)	144 (51.2)	5 (9.8)	
Synchronous liver metastasis	217 (65.4)	176 (62.6)	41 (80.4)	0.014
Bilateral liver metastasis	181 (54.5)	157 (55.9)	24 (47.1)	0.245
Estimated liver involvement				0.662
< 50%	58 (17.5)	48 (17.1)	10 (19.6)	
≥ 50%	274 (82.5)	233 (82.9)	41 (80.4)	
Tumor grade				0.015
Well-differentiated	129 (57.1)	122 (59.5)	7 (33.3)	
Moderately differentiated	53 (23.5)	48 (23.4)	5 (23.8)	
Poorly differentiated	44 (19.5)	35 (17.1)	9 (42.9)	
NA/missing	106	76	30	
Extrahepatic disease	37 (11.1)	30 (10.7)	7 (13.7)	0.524
Preoperative treatment				0.218
Octreotide	22 (6.6)	20 (7.1)	2 (3.9)	
Chemotherapy	27 (8.1)	20 (7.1)	7 (13.7)	
None	283 (85.2)	241 (85.8)	42 (82.4)	
Intraoperative ablation	76 (22.9)	69 (24.6)	7 (13.7)	0.090
Type of hepatectomy				0.019
Parenchymal-sparing resection	205 (61.7)	181 (64.4)	24 (47.1)	
Major resection	127 (38.3)	100 (35.6)	27 (52.9)	
Margin				0.030
R0/R1	291 (87.7)	251 (89.3)	40 (78.4)	
R2	41 (12.3)	30 (10.7)	11 (21.6)	
Adjuvant therapy	129 (38.9)	114 (40.6)	15 (29.4)	0.133

Data are expressed as *n* (%) unless otherwise specified

IQR interquartile range, NA not available

patients and metachronous in 115 (34.6%) patients. Bilateral liver disease was present in the majority of patients (*n* = 181, 54.5%) and most patients had an estimated ≥ 50% liver involvement (*n* = 440, 79.4%). Extrahepatic metastatic disease was noted in 37 (11.1%) patients at the time of liver surgery. Most patients (*n* = 283, 85.2%) did not receive any additional treatment before hepatectomy, while 22 (6.6%) and 27 (8.1%) patients had received octreotide or chemotherapy, respectively. Most patients (*n* = 205, 61.7%) underwent a parenchymal-sparing resection. During the operation, tumor ablation was concomitantly performed in 76 (22.9%) patients. On final pathology, 291 (87.7%) patients had a curative-intent resection (R0/R1), while 41 (12.3%) patients had a macroscopically positive (R2) surgical

margin. The majority of patients (*n* = 203, 61.1%) did not receive any adjuvant treatment, whereas 129 (38.9%) patients received postoperative octreotide or chemotherapy.

Overall Survival (OS): Primary Resected Versus Unresected Non-functional Neuroendocrine Liver Metastasis (NF-NELM)

Among the 332 patients with NF-NELM, the primary tumor was resected in 281 (84.6%) patients; 51 (15.4%) patients had an unresected primary tumor at the time of liver surgery for NELM (Fig. 1). The 1-, 3-, 5-, and 10-year survival of the entire cohort was 97.4, 89.5, 82.2, and 65.1%, respectively. Patients who had a resected primary

tumor were more likely to be male (56.9% vs. 41.2%, $p = 0.038$) and have a pancreatic NET (51.2% vs. 9.8%, $p < 0.001$) versus patients who had a primary NET that was not resected (Table 1). More patients with an unresected primary tumor presented with a synchronous liver metastasis compared with patients who had the primary NET resected (80.4% vs. 62.6%, $p = 0.014$). Although tumor burden was not different among patients with a resected versus unresected primary tumor ($\geq 50\%$ liver involvement, 82.9% vs. 80.4%, $p = 0.662$), patients who had the primary tumor resected were more likely to undergo parenchymal-sparing hepatic resection (64.4% vs. 47.1%, $p = 0.019$) and had a higher incidence of curative-intent resection (R0/R1, 89.3% vs. 78.4%, $p = 0.030$) versus patients with an unresected primary tumor (Table 1). Patients with a primary resected tumor were more likely to have a well-differentiated tumor (59.5%), while patients with a primary unresected tumor were more likely to have a poorly differentiated tumor (42.9%, $p = 0.015$). Lymph node metastasis was present in 105 (37.4%) patients.

Patients who underwent primary NET resection had a comparable long-term OS versus patients who had an unresected NET primary (10-year survival rate, primary resected 66.8% vs. unresected 54.0%, $p = 0.192$) [Fig. 2a]. The propensity-matched cohort included 90 patients who did or did not have the primary NET resected (Electronic Supplementary Table 1). In the matched cohort, OS was equivalent among patients who had the primary NET resected versus patients who had an unresected primary NET (10-year survival rate, primary resected 75.7% vs. unresected 60.4%, $p = 0.271$) [Fig. 2b]. Of note, no

differences in OS were identified among patients undergoing hepatic resection for NF-NELM among the different eras (1980–2000 vs. 2001–2010 vs. after 2011, $p = 0.396$) [Electronic Supplementary Fig. 1].

OS: Presence of Extrahepatic Metastatic Disease Versus Intrahepatic-Only Metastasis

At the time of NF-NELM resection, extrahepatic metastatic disease was noted in 37 (11.1%) patients (Fig. 1). Extrahepatic sites included the lungs ($n = 11$), peritoneum ($n = 19$), bone ($n = 7$), and other sites ($n = 12$); 9 patients had multiple sites of extrahepatic metastases. Compared with patients who had intrahepatic-only disease, patients with NF-NELM plus extrahepatic metastasis were more likely to have a pancreatic primary tumor (47.5% vs. 24.3%, $p = 0.008$) [Electronic Supplementary Table 2]. Patients with extrahepatic metastatic disease had a worse OS versus patients with intrahepatic-only metastasis (10-year survival rate, 69.3% vs. 37.5%, $p = 0.002$) [Fig. 3a]. After 1:2 PSM, the analytic cohort included 95 patients who had comparable demographic and clinicopathologic characteristics (Electronic Supplementary Table 2). In the matched cohort, the presence of extrahepatic metastatic disease remained associated with worse long-term outcome (10-year survival, extrahepatic metastatic disease 36.3% vs. intrahepatic-only disease 77.9%, $p = 0.019$) [Fig. 3b].

Risk Factors Associated with OS of NF-NELM

On univariate analysis, symptomatic, pancreatic primary NET, synchronous liver metastasis, R2 resection, tumor

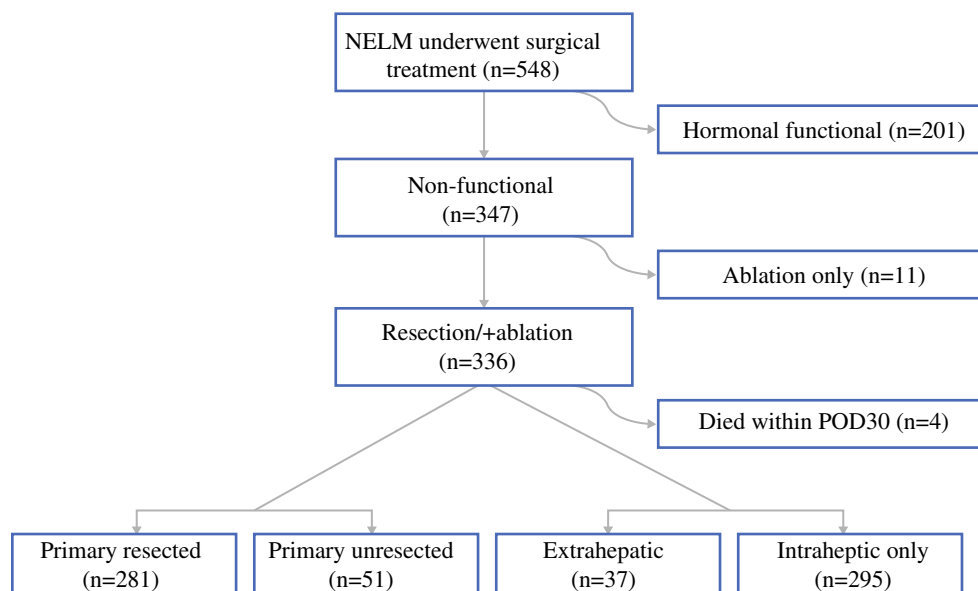


FIG. 1 Patient inclusion and study scenario. *NELM* neuroendocrine liver metastasis, *POD* postoperative day

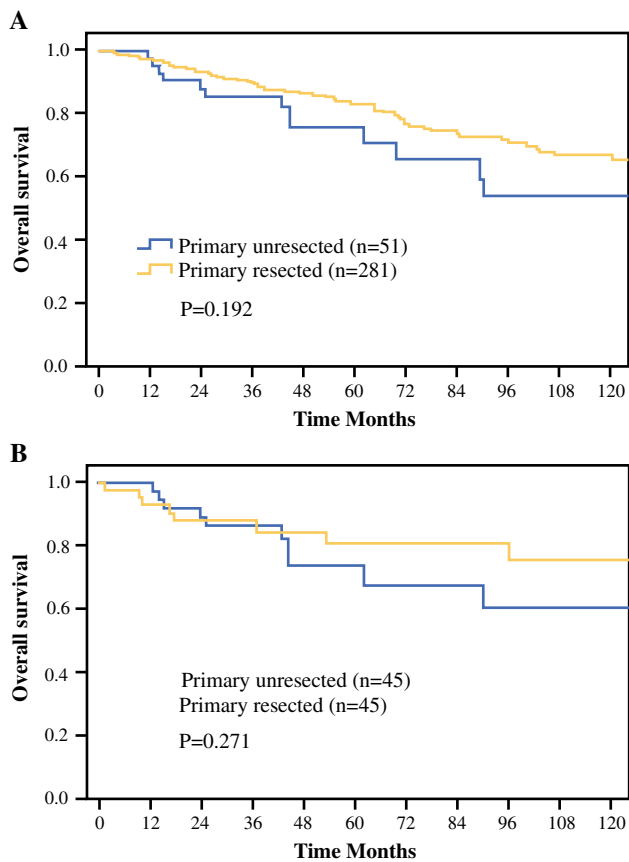


FIG. 2 Overall survival after curative-intent surgery for primary resected and unresected non-functional neuroendocrine liver metastasis before (a) and after (b) propensity score matching

grade, and extrahepatic metastatic disease were each associated with worse long-term survival among patients with NF-NELM (Table 2). Of note, resection of the primary NET was not associated with OS (HR 0.7, 95% CI 0.4–1.2, $p = 0.195$). On multivariable analysis, after taking into account all potential confounding factors, the presence of extrahepatic metastatic disease (HR 3.9, 95% CI 1.7–9.2, $p = 0.002$) remained independently associated with worse outcome among patients with NF-NELM.

DISCUSSION

With improvements in abdominal imaging, the incidence of NF-NETs has increased to 50–75% of all GEP-NETs.¹⁶ In fact, over half of NF-NET patients are asymptomatic and have disease sporadically discovered on imaging for an unrelated problem.^{14,17,18} Due to occult progression and delayed diagnosis, more NF-NET patients may present with an unresectable primary tumor and extrahepatic metastasis than patients with functional NETs.^{14,17,18} In turn, the presence of unresectable primary NETs and/or extrahepatic metastasis are still considered a

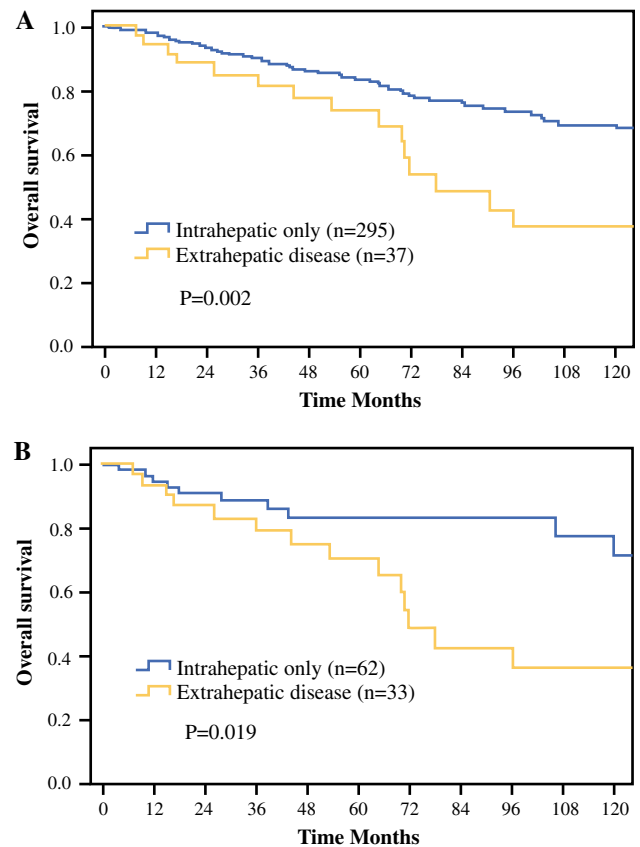


FIG. 3 Overall survival of non-functional neuroendocrine liver metastasis patients with or without extrahepatic metastatic disease before (a) and after (b) propensity score matching

contraindication to surgery by many clinicians.^{11,19} However, aggressive onco-surgery has been increasingly advocated, even in the presence of advanced metastatic disease.^{20,21} The current study was important as it specifically defined the outcomes of patients with advanced NF-NELM who had unresected primary NETs, as well as extrahepatic metastasis using a large, international, multi-institutional database. Of note, long-term survival was comparable among patients who had the primary NET resected versus patients who had an unresectable primary NET left in situ. Comparable long-term OS among patients who did and did not have the primary NET resected was noted on both unadjusted (10-year survival rate 66.8% vs. 54.0%, $p = 0.192$) and adjusted (10-year survival rate 75.7% vs. 60.4%, $p = 0.271$) analyses. In contrast, the presence of extrahepatic metastatic disease was strongly associated with a worse OS compared with intrahepatic-only disease as patients who had extrahepatic metastatic disease were noted to have a 2.5-fold higher risk of death long-term.

The beneficial role of resecting the primary NET has been a topic of debate. Givi et al. reported on 84 patients with gastrointestinal carcinoid hepatic metastases and

TABLE 2 Risk factors associated with overall survival rate of non-functional neuroendocrine liver metastasis

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> Value	HR (95% CI)	<i>p</i> Value
Age, ≤ 60/> 60 years	0.9 (0.6–1.4)	0.613		
Sex, male/female	1.5 (0.9–2.4)	0.089		
Symptomatic	1.7 (1.0–2.7)	0.030	1.6 (0.8–2.9)	0.158
Primary tumor location		0.005		0.002
Non-pancreatic	Ref.		Ref.	
Pancreatic	1.9 (1.2–3.1)		2.8 (1.4–5.4)	
Primary tumor resected	0.7 (0.4–1.2)	0.195		
Synchronous liver metastasis	2.5 (1.5–4.2)	< 0.001	2.1 (1.0–4.1)	0.037
Bilateral liver metastasis	0.9 (0.6–1.5)	0.758		
Estimated liver involvement, < 50%/≥ 50%	0.9 (0.5–1.6)	0.727		
Tumor grade				
Well-differentiated	Ref.		Ref.	
Moderately differentiated	4.0 (2.0–8.0)	< 0.001	3.0 (1.5–6.1)	0.003
Poorly differentiated	4.1 (2.0–8.4)	< 0.001	2.2 (0.9–5.2)	0.067
Extrahepatic disease	2.4 (1.3–4.1)	0.002	3.9 (1.7–9.2)	0.002
Preoperative treatment				
None	Ref.			
Octreotide	0.8 (0.2–2.4)	0.650		
Chemotherapy	1.7 (0.8–3.6)	0.197		
Intraoperative ablation	1.2 (0.7–2.0)	0.516		
Types of hepatectomy		0.088		
Parenchymal-sparing resection	Ref.			
Major resection	0.7 (0.4–1.1)			
Margin		< 0.001		0.027
R0/R1	Ref.		Ref.	
R2	3.9 (2.2–6.9)		2.5 (1.1–5.6)	

HR hazard ratio, CI confidence interval, Ref. reference

noted that primary tumor resection was associated with improved survival.²² However, all patients in this study received non-surgical treatment for NELM.²² Whether there is a role for surgical resection of NF-NELM in the setting of an unresected primary NET remains largely unknown. Importantly, data from the current study demonstrated comparable long-term survival among patients who did and did not have the primary NET resected. In fact, the presence of an unresected primary NET was not a risk factor for OS among patients undergoing resection of NF-NELM. As such, hepatic resection of NF-NELM should be strongly considered, even in the setting of an unresectable primary NET tumor.

According to the European Neuroendocrine Tumor (ENET) system, as well as other investigators, the presence of extrahepatic metastatic disease is a strong negative prognostic factor and should be considered a relative contraindication to surgery among patients with NELM.^{8,9,23,24} In the current study, patients with extrahepatic metastasis who underwent resection of NELM had a more than twofold increased risk of death long-term.

Interestingly, the 10-year survival of patients with extrahepatic NET disease who underwent resection of NELM was still almost 40%. Whether patients with non-functional NET who have extrahepatic metastatic disease and extensive NELM benefit from surgery is controversial. Mayo et al. reported on patients with NELM who were treated with surgery versus intra-arterial therapy (IAT) and noted an overall improved survival with surgery.²³ However, among patients who had an NF-NET and large (> 50%) liver involvement, there was no difference in survival among patients who underwent resection versus IAT.²³ Similarly, Kennedy et al. reported the benefit of Y-90 microsphere therapy in the treatment of patients with advanced NETs.²⁵ Overall, the presence of extrahepatic metastatic disease has been reported to have a varied effect on long-term prognosis relative to the extent of liver disease.^{12,13,26,27} In one study using the Surveillance, Epidemiology, and End Results (SEER) database, Franko et al. examined patients with non-functional PNETs and reported that while distant metastasis was a negative prognostic marker, surgical resection improved the long-

term outcome of patients with distal metastasis versus non-surgical treatments.⁶ However, given the limitations of the SEER dataset, this study had no clear classification of what constituted a 'true' distant metastasis.⁶ Collectively, the data would suggest that hepatic resection of NF-NELM may be reasonable in the presence of low-volume extrahepatic disease.^{8,28} However, given the higher risk of poor long-term outcomes defined in the current study, patients with a large burden of intra- and extrahepatic disease may not derive a strong benefit from surgery, and less invasive therapeutic approaches such as IAT should be considered.

The current study had several limitations. The multi-institutional nature of the cohort allowed for an increased sample size to examine a relatively rare disease, yet selection criteria for surgery among different centers may have been inconsistent, and the heterogeneity of the patient population may have allowed for certain biases. In addition, only patients who underwent hepatic resection for NF-NELM were included in the current database; therefore, 'control' patients who were untreated or received non-surgical treatment were not available for comparison purposes. As such, the survival benefit of resection versus nonsurgical treatments among patients with presence of primary unresected or extrahepatic metastatic disease might be limited in the current study, which needs to be further evaluated.

CONCLUSIONS

At the time of surgical treatment for NF-NELM, approximately 1 of 7 and 1 of 10 patients presented with an unresectable primary tumor and/or extrahepatic disease, respectively. Patients with primary unresected NET had a comparable survival versus patients who had the primary NET resected. In contrast, survival among patients with extrahepatic metastatic disease was worse versus patients who had intrahepatic-only disease. While surgery should be considered for patients with NF-NELM who have an unresectable primary tumor, operative resection of NF-NELM may not be as beneficial in patients with extrahepatic disease.

ACKNOWLEDGMENT Jun-Xi Xiang and Xu-Feng Zhang were supported by the Clinical Research Award of the First Affiliated Hospital of Xi'an Jiaotong University of China (No. XJTU1AF-CRF-2017-004).

AUTHOR CONTRIBUTIONS Study design: J.X. Xiang, X.F. Zhang, T.M. Pawlik. Data collection and interpretation: E.W. Beal, L. Aldrighetti, G.A. Poultsides, T.W. Bauer, R.C. Fields, S.K. Maithel, H.P. Marques, M. Weiss. Data analysis: J.X. Xiang, X.F. Zhang. Drafting of the manuscript: X.J. Xiang, X.F. Zhang. Revision of the draft version of the manuscript: X.F. Zhang, T.M. Pawlik.

CONFLICTS OF INTEREST None declared.

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